Antiphospholipid Syndrome: Update

Monica Galli, MD, PhD

Address: Divisione di Ematologia
Ospedali Riuniti
L.go Barozzi, 1
24128, Bergamo
Tel: 035 269 492
Fax: 035 266 164
e-mail: monicagalli@virgilio.it
monicagalli@ospedaliriuniti.bergamo.it

The Antiphospholipid Syndrome (APS) is defined by the association of arterial and/or venous thrombosis and/or pregnancy complications with the presence of at least one among the main antiphospholipid antibodies (aPL) (i.e., Lupus Anticoagulants, LA, IgG and/or IgM anticardiolipin antibodies, aCL, IgG and/or IgM anti-2-glycoprotein I antibodies, a-2-GPI). Since the clinical events are relatively common in the general population and they do not have distinctive features, the presence of aPL is an absolute requirement for the correct diagnosis of APS. In 2006 the clinical and laboratory criteria of APS have been updated. Details have been provided regarding aCL and a-2-GPI isotypes and titers as well as timing of antibody determination. The criteria for LA testing have been updated in 2009.

At present, the three aPL have the same role and "dignity" as laboratory criteria for APS. However, several clinical studies have consistently reported that LA is a stronger risk factor for both arterial and venous thrombosis compared to aCL and a-2-GPI. It is also emerging the concept that -2-GPI-dependent LA – i.e., the antibody that exerts its anticoagulant effect via recognition of the Gly40-Arg43 sequence on domain I of -2-GPI - is particularly associated with the risk of thrombosis. In contrast, the -2-GPI-independent LA, which is commonly caused by antiprothrombin antibodies, does not increase the patients' risk of thrombosis. The epidemiological association between aPL antibodies and APS-related clinical events does not necessarily imply a pathogenetic link, as these antibodies could only be a useful marker of thrombosis and/or obstetric complications. A large body of studies, however, provides evidence that aPL antibodies are pathogenic. Evidence, in fact, has been given of: 1. imbalance of pro- and anti-thrombotic mechanisms towards a hypercoagulable state (such as increased resistance to annexin 5, increased resistance to activated protein C pathway, increased concentration of activated von Willebrand factor, upregulation of tissue factor and tissue factor pathway inhibitor) in patients suffering from APS; 2. in vitro activation of target cells (such as neutrophils, monocytes, endothelial cells and platelets) upon exposure to human IgG containing aPL antibodies or to purified human a-2-GPI antibodies; 3. enhancement of venous and arterial thrombosis and development of obstetric complications upon passive injection of human IgG containing aPL antibodies or purified human aPL antibodies in animal models of thrombosis; 4. increased rate of fetal resorption in mouse models of SLE and APS.

Asymptomatic aPL-positive subjects do not require primary thromboprophylaxis, because their risk of first thrombosis is < 1% patients/year. They require, however, prophylaxis in all situations at increased risk of thrombosis and the abolishment/control of all the known acquired risk factors of thrombosis. Venous thromboembolism is the most common initial clinical manifestation of APS, occurring in 32% of patients. The initial treatment consists of unfractionated or low-molecular-weight heparin for at least 5 days, overlapped with warfarin therapy administered to achieve a target INR of 2.0 to 3.0. Indefinite anticoagulation is recommended. Patients who suffer from a first arterial thrombosis (mostly represented by cerebral ischemia) have an annual rate of (venous or arterial) recurrence of approximately 11%, irrespective of treatment with warfarin (PT INR 1.4-2.8) o aspirin (325 mg/die). The risk of recurrent thrombosis ranges from 10% to 67% per year among APS patients who have discontinued antithrombotic treatment. Recurrent thrombosis in APS tends to have the same vascular distribution as the original event.

Catastrophic APS (CAPS) is a rare manifestation, which accounts for less than 1% of all APS. According to the preliminary criteria, its diagnosis requires the evidence of involvement of three or more organs, systems and/or tissues, the simultaneous occurrence of the clinical events (or in less than one week) and their confirmation by histopathology. Aggressive antithrombotic treatment, plasma exchange, rituximab or intravenous immune globulin have been used.

Pregnancy morbidity (recurrent fetal loss, at least one fetal death or premature birth) occurs in approximately 20% of aPL-positive women. Several randomized clinical studies have shown that low molecular weight heparin with or without aspirin increases the rate of successful pregnancy outcome to approximately 80%.